Editorials

Shifting Sands in Science

THERE ARE MANY SIGNS of a lessening of public faith in science. This disturbs scientists—and physicians to the extent that they too are scientists. There is a new scrutiny of scientific research, how it is carried out, how it is reviewed, and how it is reported. There are suspicions that some scientific research may not have been as objective as had been thought, that there may have been sloppy performance and even fraud that has gone undetected, and that bias and special interests may sometimes have unduly influenced the process or the outcome. But this is not all. There are increasingly aggressive elements in the public that for one reason or another seek to impede or block scientific research in universities and elsewhere through court actions. Sometimes they even resort to overt vandalism.

These are relatively recent phenomena. One has only to look back as far as World War II, when physical science and medical science came into the public view as never before. Through the Manhattan Project, physical science dramatically and abruptly ended that war with just two atom bombs. And during the war there were unprecedented advances in medicine and surgery and new approaches to the care of mental stress. The public was impressed. It seemed that modern science could do almost anything. Following the war enormous amounts of money were invested in nuclear and biomedical research, and very great progress was made. But the public expectations for a safe and healthy world were not realized.

It turned out that harm as well as good can come of scientific research, whether in physics or biomedical science. It also turned out that the basic knowledge upon which modern science is built was not as firm or infallible as the public had assumed. It was not clear whether the physical world was made of particles, waves, or strings, and in medical science and health care the advice or recommendations seemed to change almost too often to be trusted as truly scientific or authoritative. The methods and processes of scientific research were obviously not well understood. Perhaps these uncertainties, together with a growing realization that unpredictable harm as well as unpredictable good can come from many kinds of scientific research, are what has led to a growing uneasiness or discomfort on the part of many with science. In any case, and for whatever reason, it is clear that science and the methods of science are coming under increasing scrutiny.

The scrutiny is, of course, human scrutiny, usually by nonscientists, and one of the places it is clearly evident is in medicine and health care, where it begins with patients, goes on to the third parties in health care, then to the public, and finally to society itself. Many—perhaps most—patients have begun to play a more active role in medical decisions about their own care. Some want to direct their own care within the medical system. Others reject the medical system entirely and seek care and solace elsewhere. Third party payers scrutinize the health care given by health professionals and others and make judgments according to their own interpretations. The public, confused by the messages it gets from physicians and medical scientists, is often insecure. Society seems to have decided that medicine and health care are too important to be left to the professionals. Things are very different from the time, not so long ago, when people were comfortable with the idea that "the doctor knows best."

What is to be gleaned from all this? Perhaps medical science, and all of science for that matter, is not the rock many of us were taught to believe it was—a solid rock upon which human health and medical practice are built. Rather, it is more like the shifting sands, which may have different configurations with changing tides and changing winds. Shifting sands are not usually all that stable or trustworthy. Perhaps this is somehow sensed by patients and the public who, almost unconsciously, it seems, may be questioning or even rejecting the authority of physicians and a profession that claim to rely almost entirely on what they know or think they know of medical science. All of this is not to denigrate science or medical science, but rather to point out that there is a human component in both medicine and society that tends to examine and even to question scientists' authority. It is paradoxical that while science has made modern medicine the technologic wonder that it is, science may also be an important underlying cause of much of the criticism and distrust of the medical profession that we have today. Fortunately for physicians, their eggs are not all in one basket. They have more to give to help their patients than just their science. Perhaps more easily understood and appreciated by patients and the public are the caring and care physicians can give to those who seek their help. Caring and care have been known to be curative, as well.

MSMW

Controlling Penicillinase-Producing *Neisseria gonorrhoeae*— Does It Really Matter Anymore?

IN THIS ISSUE of THE WESTERN JOURNAL OF MEDICINE, Kenneth Kizer, MD, and his colleagues at the California Department of Health Services report on a program to control a major extended outbreak of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and make certain recommendations for clinicians and local public health officials. They attribute a reduction of 59% in the reported incidence of PPNG to their efforts.

Although Kizer and co-workers undoubtedly have given the PPNG epidemic their "best shot," the article unintentionally raises some crucial policy questions about the value of categorical gonorrhea control measures, especially those with a focus no wider than a β-lactamase-producing plasmid, during a worldwide acquired immunodeficiency syndrome (AIDS) pandemic. With this in mind, I would like to take advantage of my editorial prerogative to comment on the origins and current status of gonococcal antimicrobial resistance in the United States, the implications they hold for California's PPNG control recommendations, and the need to better coordinate control programs for all sexually transmitted diseases including human immunodeficiency virus (HIV) infections.

In 1986 the Centers for Disease Control established the long-needed Gonococcal Isolate Surveillance Project to characterize the current resistance patterns in geographic regions of the country, monitor trends in these resistance

patterns, correlate patient characteristics and behaviors with infections caused by resistant strains, and use these data to develop national treatment recommendations. By September 1987, 21 public sexually transmitted disease clinics from around the United States were submitting the first 25 male urethral specimens of gonococcal organisms each month to one of four regional laboratories for fully standardized antimicrobial susceptibility testing. Of the first 7,974 specimens, a discouraging 52% met at least one of the surveillance criteria for resistance; 2.4% were PPNG, 3.3% had high-level plasmid-mediated tetracycline resistance, and 46% of the organisms without plasmid-mediated resistance had chromosomally mediated resistance to penicillin, tetracycline, or cefoxitin (S. K. Schwarcz, MD; J. M. Zenilman, MD; D. Schnell, PhD; et al: "National Surveillance of Antimicrobial Resistance in *Neisseria gonorrhoeae*," unpublished data, 1989).

How did we arrive in this fix? From 1945 to 1954, the first decade of penicillin treatment of gonorrhea, antimicrobial resistance and treatment failures were extremely rare. Even the smallest doses of penicillin, tetracycline, or chloramphenicol eradicated the helpless gonococcus. During the next 15 years, however, the gonococcus began to reveal its remarkable genetic resiliency. The proportion of organisms requiring more than 0.05 units of penicillin per milliliter for inhibition increased from 0.67% before 1955 to 65% in 1968-1969.[1]

This trend continued through 1972 and necessitated a number of upward adjustments in the recommended dose of pencillin from an introductory 100,000 units in 1945 to 4.8 million units of procaine penicillin G in 1972, delivered in an injection volume that threatened to exceed the full capacity of some human buttocks. Likewise, single oral doses of tetracycline compatible with gastric retention became ineffective.

This kind of resistance was chromosomally mediated and resulted from the random selection of mutants from a vast gonococcal population. There are a number of chromosomal loci involved in controlling varying levels of resistance to penicillin, cephalosporins, tetracycline, and other antibiotics. The common molecular mechanism is reduced permeability of the cell's outer membrane. Until recently chromosomal resistance tended to be relative and usually could be overcome by increasing the dosage.

Following a brief reprieve in the mid to late 1970s, probably owing to the United States' disengagement from military actions in Southeast Asia and the attendant interruption of the source of a large number of relatively resistant Asian strains, the gonococcus resumed its evolutionary march towards survival in an antimicrobial world.

In 1983 a higher level of chromosomally mediated resistance to penicillin and tetracycline was described in a single-strain outbreak in Durham, North Carolina.[2] The organisms required 2.0 to 4.0 μg per ml penicillin and 4 μg per ml tetracycline for inhibition, and most patients treated with either drug did not respond. Similar strains have since been reported from 23 states.[3] Although somewhat arbitrary, all gonococcal organisms that require 1 μg per ml or more of penicillin for inhibition and that do not produce β-lactamase have been specifically designated chromosomally mediated resistant *Neisseria gonorrhoeae* (CMRNG).

In March 1976, penicillinase-producing *N gonorrhoeae* was first recognized in the United States. The mechanism of resistance was dramatically different and resulted from the acquisition of a new plasmid that carried genes for production of a β-lactamase capable of breaking the essential penicillin β-lactam ring. This circular piece of extrachromosomal DNA may have arisen in a *Hemophilus* species and is an example of successful exchange of genetic material between unrelated species.

The incidence of PPNG rose slowly through 1979, and most cases either were from Southeast Asia or could be traced to imported cases. From 1979 through 1987, however, the annual incidence increased rapidly from less than 1,000 to more than 25,000. Penicillinase-producing *N gonorrhoeae* had become endemic in many parts of the United States and was no longer restricted to prostitute-associated outbreaks in New York City, California, and Florida. In 1986 only Nevada reported no cases, and previously spared cities such as Denver experienced extended outbreaks that continue to the present. The Denver outbreak also showed a shift to a more complex endemic pattern involving two different plasmids in at least eight genetically different strains, infecting persons from all major ethnic groups in wide areas of the city.[4]

Gonococcal organisms with plasmid-mediated, high-level resistance to tetracycline—defined as requiring 16 μg per ml or more for inhibition—were first identified in 1985 in Philadelphia and Atlanta but now have been confirmed from 17 states.[5] These organisms are designated by the acronym TRNG, even though this does not indicate the plasmid nature of resistance. Although tetracycline monotherapy will almost always fail to cure TRNG, there have been few clinically important outbreaks, presumably because most cases have been treated with the Centers for Disease Control's recommended dual therapy. Unlike chromosomally mediated resistant *N gonorrhoeae,* TRNG strains are worrisome because they arose from the insertion of a streptococcal tetracycline resistance determinant into the indigenous 24.5-megadalton conjugative gonococcal plasmid, forming a new 25.2-MDa plasmid that can facilitate its own transfer to other organisms.[6,7]

Given the genetic resiliency of the gonococcus and surveillance data documenting that more than 50% of recently identified organisms express one or more types of antimicrobial resistance, how should we control resistant *N gonorrhoeae*? In September 1987, the Centers for Disease Control published "Policy Guidelines for Detection, Management, and Control of Antibiotic-Resistant Strains of *Neisseria gonorrhoeae*,"[8] which were based on the best judgment of outside experts and staff in December 1986. Unfortunately, several of the key "guidelines" quickly proved to be either unworkable or based on faulty assumptions. In particular, they assumed that communities would have precise surveillance data to properly categorize PPNG prevalence into nonendemic (<1%), endemic (1% to 3%), and hyperendemic (>3%) areas, and that the recommended multitude of different stepped control elements were somehow appropriate to the control task. Even for the few large metropolitan areas with adequate morbidity data to determine monthly PPNG prevalence within reasonable confidence intervals, there were no empiric data to support the use of "less than 1%," "1% to 3%," and "more than 3%" divisions. More important, the assumption that PPNG prevalence, in turn, could be used as a surrogate for all types of antimicrobial resistance in areas where susceptibility testing is not available has not been supported by the findings of the Gonococcal Isolate Surveil-

lance Project (S. K. Schwarcz, MD; J. M. Zenilman, MD; D. Schnell, PhD; et al: unpublished data, 1989). The strong correlation between the presence of β-lactamase plasmids and chromosomally mediated resistance documented in the initial strains from Asia simply has been lost during the past decade of prolific genetic reshuffling.

Does controlling PPNG really matter anymore? Probably very little as an isolated program. In most areas these strains still account for only a small proportion of antimicrobial resistance. Furthermore, most antibiotics remain active against PPNG because the plasmid-specified β-lactamase hydrolyzes only penicillin and ampicillin, antibiotics that have become obsolete in the treatment of gonorrhea in much of the world. Therefore, PPNG may be less deserving of a "public health emergency" declaration and control program than many non-PPNG strains. The most important control element in the California program was the broad use of ceftriaxone, 125 mg or 250 mg given intramuscularly, which is effective at all sites of infection and against all types of resistance. It should be used wherever there is insufficient information to rule out the presence of resistant strains. A dead gonococcus cannot produce resistant progeny.

Was the California program responsible for a 59% reduction in PPNG incidence? Probably not, but without a well-matched contemporaneous control group (an unreasonable requirement) we will probably never know. Confounding variables include changes in sexual behavior of the host—such as fewer sexual partners, an increased use of condoms, and so forth—and rising levels of immunity to a recently introduced strain.[9] The epidemic curves for outbreaks of PPNG during 1986 to 1988 in Seattle[10] and other areas of the United States look quite like Figure 2 (Kizer and co-workers' article) of the California epidemic, even though specific control efforts differed or did not exist.

Finally, and most important, there is the policy issue of optimal relationships between control programs for the "traditional" sexually transmitted diseases like gonorrhea and the less traditional but more deadly HIV infections. The gonorrhea epidemic in the United States has rapidly contracted down around heterosexual poor urban minorities who have high rates of illicit drug use and prostitution to support these habits and therefore are at greatest risk of contracting HIV infections. Handsfield and associates reported that at one point during a 1987 PPNG epidemic in Seattle, an extraordinary 82% of patients gave histories of using crack or intravenous drugs or of having sexual contact with drug users.[10] At about the same time, the prevalence of HIV infections in heterosexual intravenous drug users in San Francisco increased to 12% (24% in blacks) from 6% in 1983-1984.[11] It is likely that similar HIV prevalence rates would have been found in Los Angeles patients with PPNG in 1987-1988. Until the common underlying risk behavior can be altered, the prospects for lasting control of either PPNG or HIV epidemics will remain dim. It is a hollow victory to cure someone of PPNG infection who later dies of AIDS.

Ideally, a gonorrhea epidemic—PPNG or non-PPNG—centered in poor Los Angeles minorities would be a biologic red light signaling a continuing high risk of HIV transmission and leading to a coordinated response that included not only treatment with ceftriaxone but HIV counseling, testing, and treatment; partner notification; and illicit drug counseling and treatment. The California Department of Health Services is certainly no different from most health jurisdictions throughout the world in failing to effectively integrate limited sexually transmitted disease and HIV prevention resources.

FRANKLYN N. JUDSON, MD
Director, Denver Public Health Department
Chief, Infectious Diseases
Denver General Hospital and Medical Center
Professor of Medicine and Preventive Medicine
University of Colorado Health Sciences Center
Denver

REFERENCES

1. Martin JE Jr, Lester A, Price EV, et al: Comparative study of gonococcal susceptibility to penicillin in the United States, 1955-1969. J Infect Dis 1970; 122:459-461

2. Faruki H, Kohmescher RN, McKinney WP, et al: A community based outbreak of infection with penicillin-resistant *Neisseria gonorrhoeae* not producing penicillinase (chromosomally mediated resistance). N Engl J Med 1985; 313:607-611

3. Rice RJ, Biddle JW, JeanLouis YA, et al: Chromosomally mediated resistance in *Neisseria gonorrhoeae* in the United States: Results of surveillance and reporting, 1983-1984. J Infect Dis 1986; 153:340-345

4. Centers for Disease Control (CDC): Multiple strain outbreak of penicillinase-producing *Neisseria gonorrhoeae*—Denver, Colorado, 1986. MMWR 1987; 36:534-543

5. Knapp JS, Zenilman JM, Biddle JW, et al: Frequency and distribution in the United States of strains of *Neisseria gonorrhoeae* with plasmid-mediated, high-level resistance to tetracycline. J Infect Dis 1987; 155:819-822

6. Morse SA, Johnson SR, Biddle JW, et al: High-level tetracycline resistance in *Neisseria gonorrhoeae* is a result of acquisition of streptococcal *tet*M determinant. Antimicrob Agents Chemother 1986; 30:664-670

7. Roberts MC, Knapp JS: Host range of the conjugative 25.2-megadalton tetracycline resistance plasmid from *Neisseria gonorrhoeae* and related species. Antimicrob Agents Chemother 1988; 32:488-491

8. CDC: Antibiotic-resistant strains of *Neisseria gonorrhoeae:* Policy guidelines for detection, management, and control. MMWR 1987; 36 (suppl 5S)

9. Plummer FA, Brunham RC: Gonococcal recidivism, diversity, and ecology. Rev Infect Dis 1987; 9:846-850

10. Handsfield HH, Rice RJ, Roberts MC, et al: Localized outbreak of penicillinase-producing *Neisseria gonorrhoeae*—Paradigm for introduction and spread of gonorrhea in a community. JAMA 1989; 261:2357-2361

11. Chaisson RE, Bacchetti P, Osmond D, et al: Cocaine use and HIV infection in intravenous drug users in San Francisco. JAMA 1989; 261:561-565

The Clinical Dilemma of Psychotropic Drug Use During Pregnancy

THIS MONTH'S ISSUE includes an important and timely review by Guze and Guze of the use of psychotropic medication during pregnancy.

This clinical dilemma is a common one in that as many as 80% of pregnant women take prescribed drugs and up to 35% take a psychoactive drug.[1,2] Clinicians, however, must rely mostly on data from animal studies and suboptimal epidemiologic studies in humans for guidance. In their review Guze and Guze make several important points that are useful in decision making about psychotropic medications during pregnancy.

The authors remind us that it is more often a woman already taking psychotropic medications who becomes expectedly or unexpectedly pregnant rather than a woman already pregnant for whom psychotropic medications must be prescribed. This speaks to the critical importance of counseling a patient about safe and effective contraception if she will be taking a medication potentially toxic to her fetus.

The authors highlight the fact that risks to the fetus include not only structural teratogenic effects, direct toxic effects, and withdrawal effects but also long-term neurobehavioral effects. Such psychoteratogenicity may be expressed as disturbed psychomotor activity, faulty adaptation to the extrauterine environment, abnormal learning or problem-solving capacity, or other subtle cognitive deficits and mood disturbances. Clinicians should be aware that knowledge in this area is inadequate, and the implications for exposed